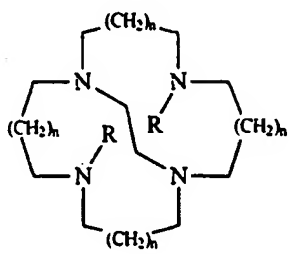




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US99/27316 (22) International Filing Date: 18 November 1999 (18.11.99) (30) Priority Data: 60/110,309 30 November 1998 (30.11.98) US (71) Applicant (for all designated States except US): THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): HILER, George, Douglas, II [US/US]; 224 Countrytrace Drive, Harrison, OH 45030 (US). PERKINS, Christopher, Mark [US/US]; 7230 Fernbank Avenue, Cincinnati, OH 45233 (US). (74) Agents: REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217-1087 (US).		(81) Designated States: AE, AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), DM, EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: PROCESS FOR PREPARING CROSS-BRIDGED TETRAAZA MACROCYCLES (57) Abstract <p>The present invention relates to a process for preparing a cross-bridged tetraaza macrocyclic ligand having formula (I) wherein each R is independently C₁-C₈ linear or branched alkyl, -(CH₂)_xCO₂M, and mixtures thereof; provided both of the R units are not methyl; M is hydrogen or a salt forming cation; x is from 1 to 6; each index n is independently from 0 to 3; by contacting a di-quaternary <i>cis</i> tetracycle precursor with hydrogen in the presence of a palladium catalyst in an aqueous solution having a pH of at least about 10 at a temperature of about 40 °C to about 100 °C.</p> <div style="display: flex; align-items: center; justify-content: center;">  <div style="margin-left: 20px;"> (I) </div> </div>		

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PROCESS FOR PREPARING CROSS-BRIDGED
TETRAAZA MACROCYCLES

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FIELD OF THE INVENTION

The present invention relates to an improved process for preparing cross-bridged tetraaza
macrocycles, said macrocycles suitable as ligands for use in preparing transition metal
complexes. The present invention provides a process which is well suited for use in industrial
10 and other commercial preparations of the herein described crossed-bridged macrocycles.

BACKGROUND OF THE INVENTION

Tetraaza macrocyclics, for example, cyclam, have been prepared in numerous ways,
however, there is a paucity of information relating to the preparation of cross-bridged tetraaza
15 macrocyclics *inter alia* bis N-substituted tetraaza macrocyclics *inter alia* 5,12 dialkyl 1,5,8,12-
tetraaza-bicyclo[6.6.2]hexadecanes which have recently found wide applicability as ligands
especially in the area of transition metal catalysts *inter alia* bleach catalysts.

WO 98/39335 A1 "Improved Methods of Making Cross-Bridged Macropoly-cycles"
discloses a rational procedure for preparing cross bridged macropolycyclic ligands which is
20 amenable to high yields necessary for industrial scale-up. However, the reductive ring cleavage
step which results in bicyclo bridged-ring formation utilizes a borohydride reducing agent. This
type of reducing agent can place constraints on the formulator. For example, the need to break up
the amine/borohydride complex during work-up and the proper recovery and disposal of boron
waste products adds cost to the process. Also, if excess borohydride is needed, this requires
25 neutralization which involves the use of acid and the evolution of large quantities of hydrogen
gas.

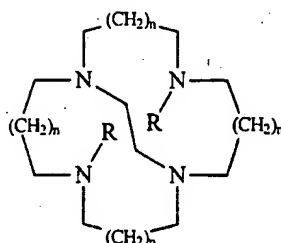
Therefore, a need exists for a highly quantitative, preferably catalytic, process for
preparing cross-bridged macropolycyclic ligands which is adaptable to either continuous flow
processes or batch preparations.

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SUMMARY OF THE INVENTION

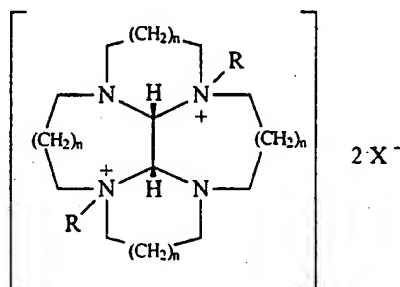
The present invention meets the aforementioned needs in that it has been surprisingly
discovered that select bis N-substituted tetraaza macrocyclics can be converted to cross-bridged
macropolycyclic ligands via catalytic hydrogenation.

A first aspect of the present invention relates to a process for preparing a tetraaza macrocyclic ligand having the formula:



- 5 wherein each R is independently C₁-C₈ linear or branched alkyl, -(CH₂)_xCO₂M, and mixtures thereof, preferably both of the R units are not methyl; M is hydrogen or a salt forming cation; x is from 1 to 6; each index n is independently from 0 to 3; said process comprising the steps of:

- a) hydrogenating a tetraaza macrocyclic ligand precursor having the formula:



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wherein X⁻ is an anion which provides charge neutrality, with from about 1 ppm of a transition metal hydrogenation catalyst at a pH of at least 8 to form a tetraaza macrocyclic ligand; and

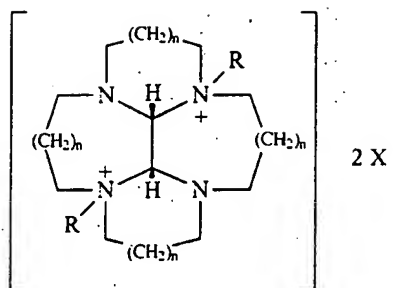
- b) optionally isolating said ligand.

- 15 These and other objects, features, and advantages will become apparent to those of ordinary skill in the art from a reading of the following detailed description and the appended claims. All percentages, ratios and proportions herein are by weight, unless otherwise specified. All temperatures are in degrees Celsius (°C) unless otherwise specified. All documents cited are in relevant part, incorporated herein by reference.

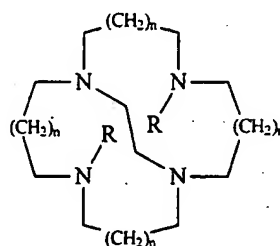
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DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the catalytic hydrogenation of tetraaza macrocycles having the formula:



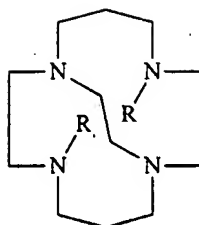
wherein the covalent bond between the N-substituted quaternary ring nitrogen and the bridging carbon is broken and a cross-bridged macrocyclic ligand having the formula:



is the resulting product.

In the above formula each R is independently C_1 - C_8 linear or branched alkyl, - $(CH_2)_xCO_2M$, and mixtures thereof, preferably both of the R units are not methyl; more preferably one R unit is methyl and the other R unit is selected from the group consisting of ethyl, propyl, butyl, pentyl, hexyl, and mixtures thereof; of the methyl/alkyl R unit mixtures preferably one R is methyl and the other R is ethyl or propyl. A most preferred ligand consists of a unit wherein one R unit is methyl and the other R unit is ethyl. A preferred ligand is a macrocyclic ring wherein each R unit is ethyl. M is hydrogen or a salt forming cation, non-limiting examples of which are sodium, potassium, calcium, ammonium. When R is $-(CH_2)_xCO_2M$ the index x has the value from 1 to about 6, preferably x is 1. The index n defines the size of the macrocyclic ring. The index n has the value of from 0 to about 3. A preferred macrocyclic ring has one opposite set of n indices equal to 1 and the other set of n indices equal to 0 as in the general formula:

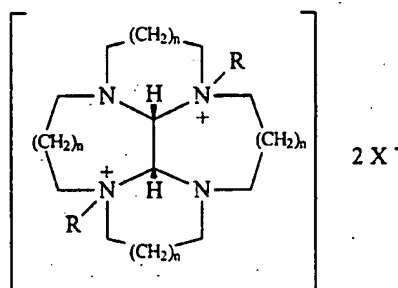
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wherein R is the same as defined herein above.

Preferred ligands according to the present invention comprise R unit pairs which are selected from the group consisting of methyl and ethyl, diethyl, methyl and propyl, ethyl and propyl, methyl and butyl, ethyl and butyl, and mixtures thereof.

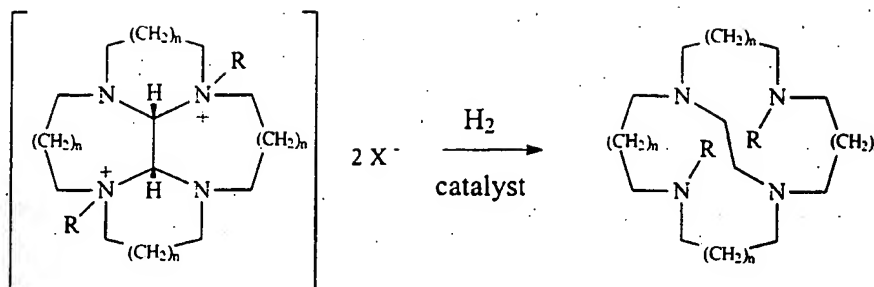
The starting materials for the process of the present invention are tetraaza macrocyclic ligand precursors, or alternatively, bis-quaternary *cis* tetracycles, having the formula:



wherein R and n are the same as defined herein above. X is an anion which serves to provide electronic neutrality to the bis-quaternary *cis* tetracycle. Those of ordinary skill in the art recognize that the term "electronic neutrality" refers to "a sufficient amount of an anionic species which satisfies the molecular charge balance requirements" and that a mixture of mono-, di-, tri-, etc. electronic species may be used herein. X preferably has unit negative charge, for example, halogen, tosylate, methylsulfate, ethylsulfate. However, X may have more than one negative charge, for example, sulfate, in which case the formulator requires only half the amount necessary when using a unit negative-charged anion. Preferred X is chloride, bromide, iodide, sulfate, ethyl sulfate, methyl sulfate, tosylate, mesylate, triflate, and mixtures thereof.

20 STEP (a) Hydrogenation - Reductive Cleavage

Step (a) comprises the reductive cleavage via catalytic hydrogenation as outlined in the following scheme:



wherein the *cis*-tetracycle bis quaternary salt is converted to the cross-bridged tetraaza macrocycle.

- Step (a) is conducted in the presence of a catalyst, preferably a supported catalyst. Non-limiting examples of catalysts include platinum on carbon, palladium on carbon (Pd/C), palladium hydroxide on carbon (Pd(OH)₂/C), rhodium on carbon (Rh/C), Raney nickel, and mixtures thereof. A preferred catalyst is Pd(OH)₂/C. The supported catalysts may comprise from about 1% to about 50% by weight of transition metal, however, the pure metal, i.e. palladium, can be used without the need for a "support", i.e., carbon. A "catalytic amount" of catalyst is sufficient to provide the reduction of step (a). For the purposes of the present invention the term catalytic amount is defined as "from about 1 ppm of a 5% by weight transition metal catalyst". However, the formulator, due to poisoning of the catalyst surface by reaction products may use more than a catalytic amount of a catalyst. The amount of catalyst used in step (a) of the present invention is preferably from about 10 ppm of a catalyst which contains from about 5% to 50% by weight, of a transition metal, more preferably from about 100 ppm, yet more preferably from about 0.1% by weight, of a transition metal supported catalyst. A reaction solution which comprises 0.1% by weight, of a transition metal supported catalyst, said catalyst comprising, for example, 10% by weight of palladium on carbon, has 0.01% transition metal or 100 ppm transition metal present.

The amount of hydrogen gas present in step (a) of the present invention need only be enough to sufficiently saturate the catalyst surface, preferably the hydrogen pressure is from 200 psi, more preferably from 400 psi, most preferably from 800 psi to about 2000 psi, more preferably to 1000 psi.

- Step (a) of the present process can be conducted at a temperature of from 20° C, preferably from about 40° C, more preferably from about 60° C to about 100° C, preferably to about 90° C, more preferably to about 80° C, most preferably to about 65° C.

The pH under which Step (a) must be conducted is at least 8, preferably at least 10, more preferably at least about 11. Preferably the base which is used to adjust the pH is in the form of an aqueous solution. Preferred bases are selected from the group consisting of potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, and mixtures thereof. As
5 a non-limiting example, it is satisfactory to use a sufficient amount of 1 M (molar) aqueous base to adjust the pH to the required level. A convenient and preferred base is potassium carbonate.

As a suitable alternative, Step (a) can be conducted in the presence of a solvent other than water, or in the absence of water. A mixture of a suitable solvent and water is a suitable means for conducting the hydrogenation process of the present invention. In the case where
10 water is absent, sufficient base must be present to stabilize the transition state of the reactants and products during hydrogenation. Non-limiting examples of solvents include methanol, ethanol, n-propanol, isopropanol, N,N-dimethyl formamide, n-butanol, iso-butanol, tert-butanol, and mixtures thereof; preferred solvents are selected from the group consisting of ethanol, n-propanol, N,N-dimethyl formamide, and mixtures thereof. When a solvent is present and the
15 base is in the form of an aqueous solution, the ratio of said volume of an aqueous base, to said solvent is from about 1:10 to about 1:1, preferably the ratio of the volume of aqueous base to solvent is 1:4. It is desirable, but not a requirement, that the aqueous base and solvent form a two phase system.

The process of the present invention comprises an optional, although preferred, Step (b) which is an isolation step. Typically this step involves filtration of the reaction solution to
20 remove the catalyst. In addition, this step may comprise a neutralization step, however, the product can be isolated or removed from the reaction matrix in any manner which the formulator desires.

When filtration of the catalyst is a desired step, the reaction solution containing the cross-
25 bridged ligand is filtered to remove the catalyst to form a crude filtrate. This crude filtrate can be neutralized or the tetraaza macrocyclic ligand can be isolated by extraction or crystallization directly from the preferably aqueous solution.

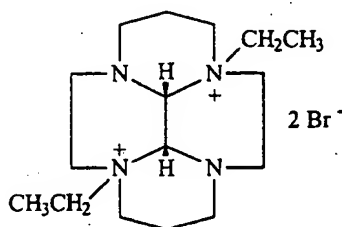
Steps (a) and (b) and any optional extensions thereto, for example, a crystallization step, a solvent drying step, a purging step, may be suitably adapted for either batch processes or
30 continuous processes, for example, continuous flow processes. As mentioned herein, the process of the present invention may comprise other optional steps as deemed necessary and/or desirable by the formulator. These optional steps may include but are not limited to, pre-saturation of the catalyst with hydrogen, drawing a vacuum on the system, and recovery of the catalyst and solvents.

Preferably the ligands formed by the process of the present invention are converted into manganese containing transition metal catalysts in a subsequent, however optional, process step. The bleach catalysts comprise a central manganese atom and a cross-branched ligand formed by the process of the present invention. The final bleach catalyst may comprise one or more other compatible ligands *inter alia* chlorine atom. The preferred catalysts are suitable as bleaching agents.

The following is a non-limiting example of the process of the present invention.

Preparation of 5,12-diethyl-1,5,8,12-tetraaza-bicyclo[6.6.2]hexadecane

To a thick walled, glass autoclave sleeve is added the bis-quaternary *cis* tetracycle having the formula:



(3.0 g, 6.8 mmol) and a 1M aqueous solution of K_2CO_3 (30 mL). The solution is agitated to dissolve the substrate then 20% $Pd(OH)_2$ /carbon (0.7 g, 1.0 mmol) is added. The glass sleeve is placed into a rocking autoclave and hydrogenated at 65° C with 1900 psig hydrogen for 4 hours. The reaction is cooled and the solution filtered through glass fiber filter paper to remove the catalyst and the filtrate is reduced to a white solid under vacuum. The white solid is suspended in refluxing ethanol and the un-dissolved inorganic salts are collected by filtration. After concentrating the filtrate under vacuum, the resulting oily residue is dissolved in aqueous 4M KOH (4 mL) and extracted three times with 25 mL portions of toluene. The toluene extracts are combined and concentrated *in vacuo* to afford 5,12-diethyl-1,5,8,12-tetraaza-bicyclo[6.6.2]hexadecane (1.56 g) in 81% yield as a clear oil.

The following is an example of an optional, but preferred step of the process of the present invention which is conversion to a manganese transition metal bleach catalyst.

Preparation of dichloro 5,12-diethyl-1,5,8,12-tetraaza-bicyclo[6.6.2]hexadecane manganese

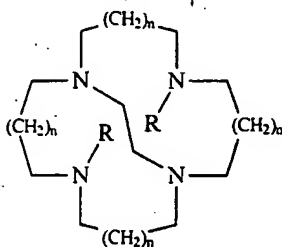
To a 100 mL reaction flask is charged anhydrous acetonitrile (50 mL) and 5,12-diethyl-1,5,8,12-tetraaza-bicyclo[6.6.2]hexadecane (1.4 g, 5 mmol). The resulting suspension is degassed under vacuum with subsequent re-filling with argon. This process is repeated six times. Manganese(II) chloride (0.590 g, 4.7 mmol) is added and the reaction is refluxed for 3 hours.

The resulting solution is filtered through glass-fiber filter paper. The resulting filtrate is concentrated under reduced pressure at 45° C to afford a solid. The solid is suspended in toluene (50 mL) and the resulting dark supernatant is discarded. Treatment with toluene is repeated five times. The resulting solid is dried under vacuum to yield dichloro 5,12-diethyl-1,5,8,12-tetraaza-

5 bicyclo[6.6.2]hexadecane manganese (1.48 g, 73% yield).

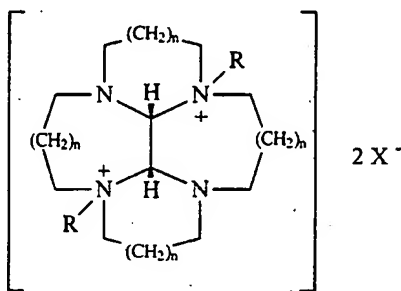
WHAT IS CLAIMED IS:

1. A process for preparing a tetraaza macrocyclic ligand having the formula:



wherein each R is independently C₁-C₈ linear or branched alkyl, -(CH₂)_xCO₂M, and mixtures thereof, provided both of the R units are not methyl; M is hydrogen or a salt forming cation; x is from 1 to 6; each index n is independently from 0 to 3; said process comprising the steps of:

- a) hydrogenating a tetraaza macrocyclic ligand precursor having the formula:



wherein X⁻ is an anion which provides charge neutrality, with from 1 ppm of a transition metal hydrogenation catalyst at a pH of at least 8 to form a tetraaza macrocyclic ligand; and

- b) optionally isolating said ligand.

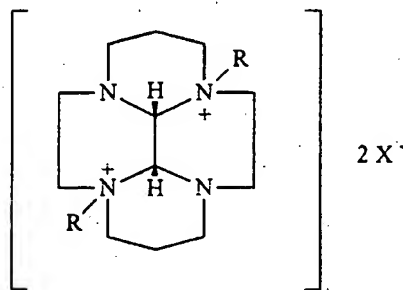
2. A process according to Claim 1 wherein said transition metal hydrogenation catalyst is selected from the group consisting of platinum, palladium, palladium hydroxide, rhodium, Raney nickel, and mixtures thereof.
3. A process according to either of Claims 1 or 2 wherein step (a) is conducted at a temperature of from 40° C to 100° C, at a pH of at least 10, and in the presence of a solvent, said solvent selected from the group consisting of water, N,N-dimethyl

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formamide, methanol, ethanol, isopropanol, n-butanol, iso-butanol, tert-butanol, and mixtures thereof.

4. A process according any of Claims 1-3 wherein said precursor has the formula:

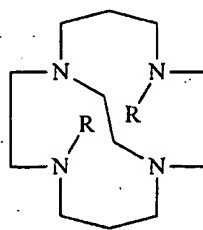
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wherein R and X are the same as defined herein above.

5. A process according to any of Claims 1-4 wherein each R is ethyl.
6. A process according to any of Claims 1-5 wherein one R is methyl and one R is ethyl.
7. A process for preparing a tetraaza macrocyclic ligand having the formula:

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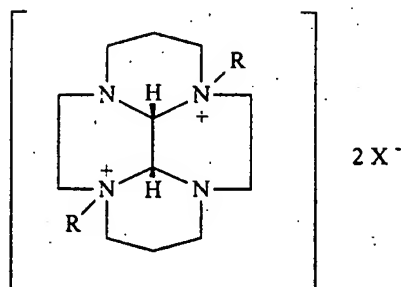
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wherein one R unit is methyl and the other R unit is selected from the group consisting of ethyl, propyl, butyl, pentyl, hexyl, and mixtures thereof; said process comprising the steps of:

- a) hydrogenating a tetraaza macrocyclic ligand precursor having the formula:

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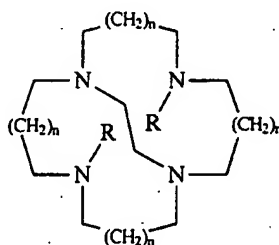
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wherein X^- is an anion which provides charge neutrality, with from 1 ppm of a palladium hydrogenation catalyst at a pH of at least 10 to form a tetraaza macrocyclic ligand; and

5 b) optionally isolating said ligand.

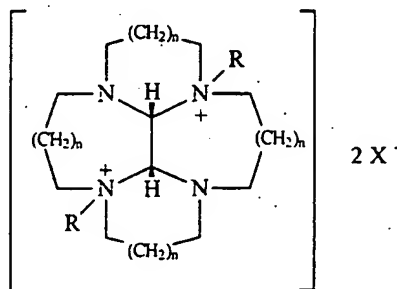
8. A process for preparing a tetraaza macrocyclic ligand having the formula:



10 wherein each R is independently C_1 - C_8 linear or branched alkyl, $-(CH_2)_xCO_2M$, and mixtures thereof, provided both of the R units are not methyl; M is hydrogen or a salt forming cation; x is from 1 to 6; each index n is independently from 0 to 3; said process comprising the steps of:

a) hydrogenating a tetraaza macrocyclic ligand precursor having the formula:

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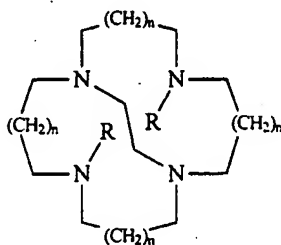


wherein X^- is an anion which provides charge neutrality, with from 1 ppm of a palladium hydrogenation catalyst, said palladium catalyst selected from the

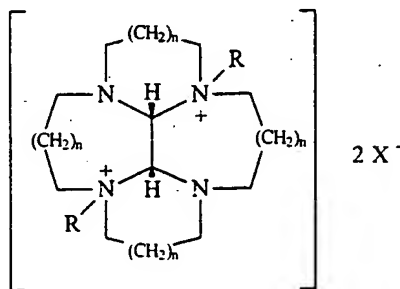
- group consisting of supported palladium(0), palladium hydroxide, and mixtures thereof; at a pH of at least 8; in the presence of a solvent, said solvent selected from the group consisting of water, methanol, ethanol, N,N-dimethyl formamide, n-butanol, iso-butanol, tert-butanol, and mixture thereof; at a temperature of from 0° C to 100° C; to form a tetraaza macrocyclic ligand; and
- 5 b) removing the catalyst by filtration to form a crude filtrate;
- c) optionally isolating said ligand by crystallizing, extracting, distilling, or other suitable means.

- 10 9. A process according to Claim 8 wherein said process further comprises the step of treating said ligand with manganese to form a cross-bridged tetraaza macrocyclic transition metal catalyst.

- 15 10. A process for preparing a tetraaza macrocyclic ligand having the formula:



- wherein R units are R unit pairs selected from the group consisting of methyl and ethyl, diethyl, methyl and propyl, ethyl and propyl, methyl and butyl, ethyl and butyl, and mixtures thereof; M is hydrogen or a salt forming cation; x is from 1 to 6; each index n is independently from 0 to 3; said process comprising the steps of:
- 20 a) hydrogenating a tetraaza macrocyclic ligand precursor having the formula:



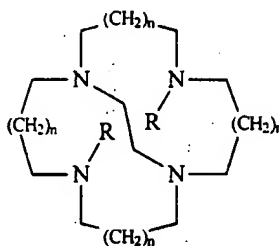
wherein X^- is an anion which provides charge neutrality, with from 1 ppm of a transition metal hydrogenation catalyst at a pH of at least 8 to form a tetraaza macrocyclic ligand; and

b) optionally isolating said ligand.

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11. A transition metal catalyst comprising:

a) a crossed-bridged ligand having the formula:



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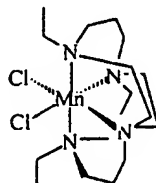
wherein each R is independently C_1 - C_8 linear or branched alkyl, $-(CH_2)_xCO_2M$, and mixtures thereof, provided both of the R units are not methyl or butyl; M is hydrogen or a salt forming cation; x is from 1 to 6; each index n is independently from 0 to 3;

b) manganese; and

15

c) optionally one or more compatible ligands.

12. A compound according to Claim 11 having the formula:

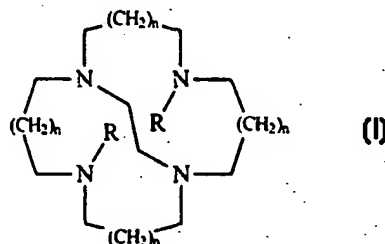


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(21) International Application Number: PCT/US99/27316 (22) International Filing Date: 18 November 1999 (18.11.99) (30) Priority Data: 60/110,309 30 November 1998 (30.11.98) US (71) Applicant (for all designated States except US): THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): HILER, George, Douglas, II [US/US]; 224 Countrytrace Drive, Harrison, OH 45030 (US). PERKINS, Christopher, Mark [US/US]; 7230 Fernbank Avenue, Cincinnati, OH 45233 (US). (74) Agents: REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217-1087 (US).		(81) Designated States: AE, AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), DM, EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> (88) Date of publication of the international search report: 5 October 2000 (05.10.00)
(54) Title: PROCESS FOR PREPARING CROSS-BRIDGED TETRAAZA MACROCYCLES (57) Abstract The present invention relates to a process for preparing a cross-bridged tetraaza macrocyclic ligand having formula (I) wherein each R is independently C ₁ -C ₈ linear or branched alkyl, -(CH ₂) _x CO ₂ M, and mixtures thereof; provided both of the R units are not methyl; M is hydrogen or a salt forming cation; x is from 1 to 6; each index n is independently from 0 to 3; by contacting a di-quaternary <i>cis</i> tetracycle precursor with hydrogen in the presence of a palladium catalyst in an aqueous solution having a pH of at least about 10 at a temperature of about 40 °C to about 100 °C.		



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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/27316

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D487/08 C07F13/00 B01J31/18 //(C07D487/08,255:00,
255:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07F B01J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 39335 A (PROCTER & GAMBLE) 11 September 1998 (1998-09-11) page 10	1
A	WO 98 39098 A (THE UNIVERSITY OF KANSAS) 11 September 1998 (1998-09-11) page 49 -page 57; claim 1	11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9839335 A	11-09-1998	AU 6226198 A EP 0971927 A	22-09-1998 19-01-2000
WO 9839098 A	11-09-1998	AU 6226498 A EP 0966323 A ZA 9801883 A	22-09-1998 29-12-1999 01-09-1998